

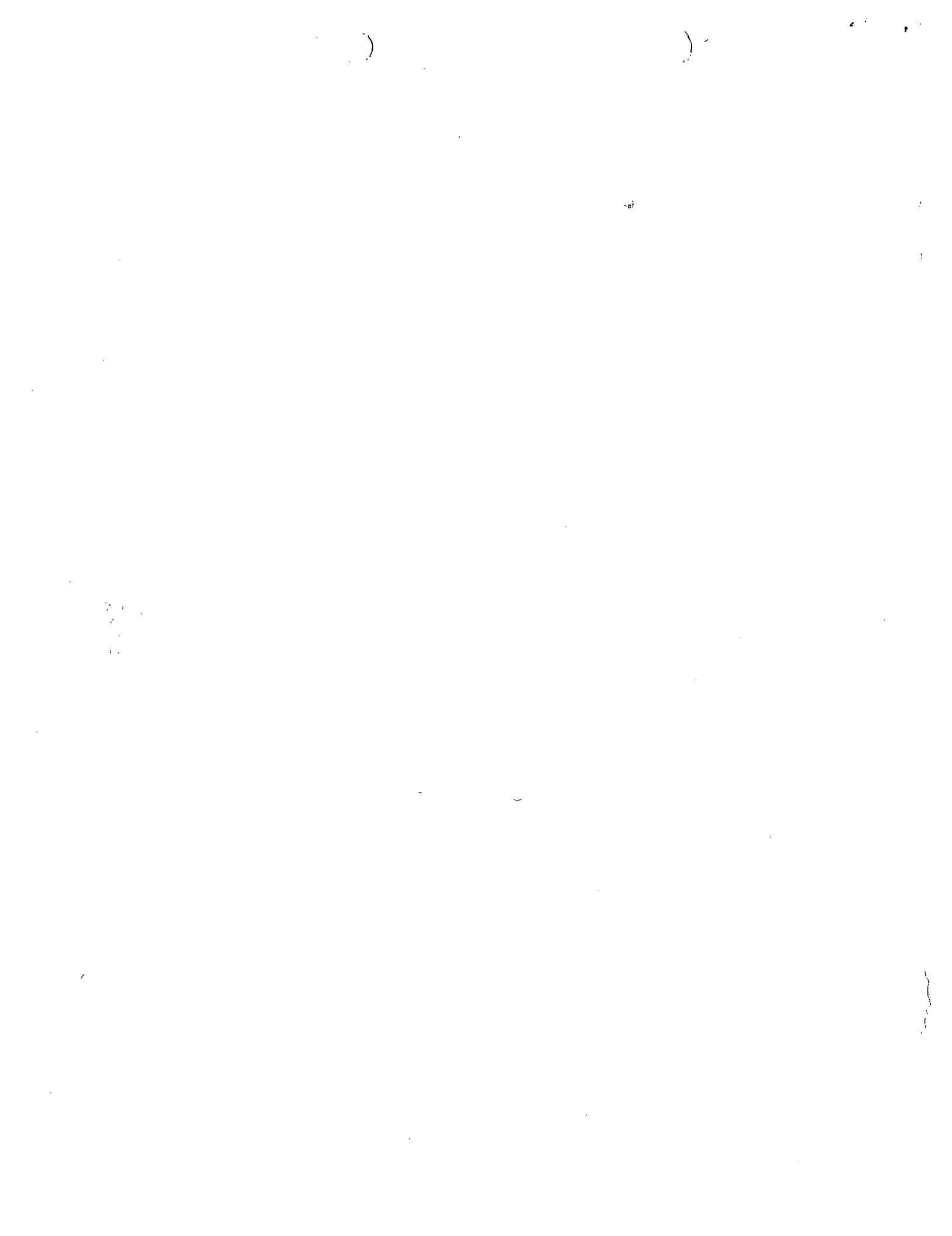
PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

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- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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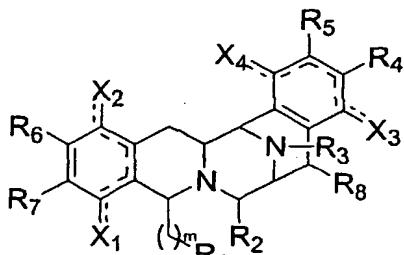
— with international search report

(88) Date of publication of the international search report: 27 February 2003

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

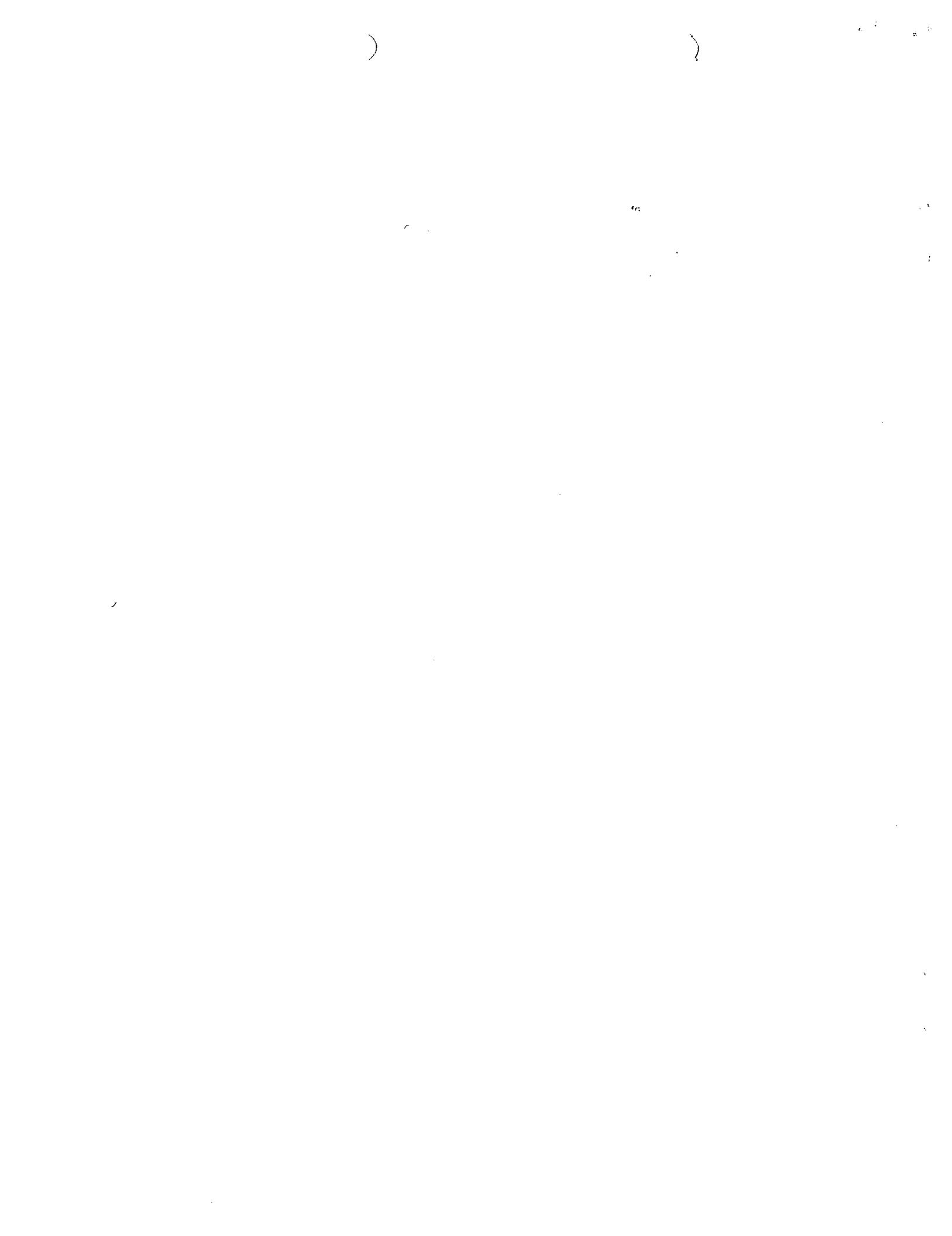
(54) Title: SAFRAMYCINS, ANALOGUES AND USES THEREOF

WO 02/040477 A3



(I)

(57) Abstract: In recognition of the need to develop novel therapeutic agents and efficient methods for the synthesis thereof, the present invention provides novel compounds of general formula (I), and methods for the synthesis thereof (I). In another aspect, the present invention provides pharmaceutical compositions comprising a compound of formula (I) and a pharmaceutically acceptable carrier. In yet another aspect, the present invention provides methods for treating cancer comprising administering a therapeutically effective amount of a compound of formula (I) to a subject in need thereof.



INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/47399

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/495 C07D471/18

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07D A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, CHEM ABS Data, BEILSTEIN Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, Y	WO 00 18233 A (HARVARD COLLEGE) 6 April 2000 (2000-04-06) page 98; claim 1 ---	1-75
X, Y	HILL ET AL.: "Computer Simulation ..." J.MED.CHEM., vol. 34, 1991, pages 1990-1998, XP002206549 Scheme II page 1991 --- -/-	1-75

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

18 July 2002

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INTERNATIONAL SEARCH REPORT

International Application No.
PCT/US 97/47399

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	MARTINEZ E J ET AL: "A NEW, MORE EFFICIENT, AND EFFECTIVE PROCESS FOR THE SYNTHESIS OF A KEY PENTACYCLIC INTERMEDIATE FOR PRODUCTION OF ECSTEINASCIDIN AND PHTHALASCIDIN ANTITUMOR AGENTS" ORGANIC LETTERS, ACS, WASHINGTON, DC, US, vol. 2, no. 7, 2000, pages 993-996, XP002940455 ISSN: 1523-7060 page 993 ---	1-75
X	MEYERS ET AL.: "One-step construction of the pentacyclic ..." ORG.LETT., vol. 2, no. 9, 23 August 2000 (2000-08-23), pages 3019-3022, XP002206550 see compounds 9,5 ---	1-5, 12-24
X	MEYERS ET AL.: "A concise, stereocontrolled synthesis..." J.AM.CHEM.SOC., vol. 121, 1999, pages 10828-10829, XP002206551 see compounds 2,10,11 ---	1-5, 12-24
X	FUKUYAMA T ET AL: "TOTAL SYNTHESIS OF (PLUS OR MINUS)-SAFRAMYCIN A" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol. 112, no. 9, April 1990 (1990-04), pages 3712-3713, XP002925425 ISSN: 0002-7863 see compounds 15 and 16 ---	1-5, 12-24
X	KUBO ET AL.: "Synthesis of saframycins..." CHEM.PHARM.BULL., vol. 35, no. 5, 1987, pages 2158-2161, XP002206552 see compounds 7,8,10-20,23 ---	1-7, 10-28, 30-32
X	PATENT ABSTRACTS OF JAPAN vol. 012, no. 202 (C-503), 10 June 1988 (1988-06-10) & JP 63 002991 A (AKINORI KUBO; OTHERS: 01), 7 January 1988 (1988-01-07) abstract ---	1-7, 10-28, 30-32

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/47399

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SAITO N ET AL: "SYNTHESIS OF SAFRAMYCINS. VII. THE SYNTHESIS OF NOVEL RENIERAMYCIN CONGENERS" HETEROCYCLES, ELSEVIER SCIENCE PUBLISHERS B.V. AMSTERDAM, NL, vol. 32, no. 6, 1991, pages 1203-1214, XP001036954 ISSN: 0385-5414 see compounds 3-8,10,11,14-15, ---	1-7, 10-28, 30-32
X	SAITO ET AL.: "Synthesis of saframycins..." TETRAHEDRON, vol. 51, no. 30, 1995, pages 8213-8230, XP002206553 compounds 9,26-33,35 ---	1-7, 10-28, 30-32
X	SAITO ET AL.: "Synthesis of saframycins..." TETRAHEDRON, vol. 51, no. 20, 1995, pages 8231-8246, XP002206554 see compounds 5,6,10a,10-16,25,26 ---	1-5, 12-24
X	FUKUYAMA T ET AL: "STEREOCONTROLLED TOTAL SYNTHESIS OF (PLUS OR MINUS)-SAFRAMYCIN B" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, XX, XX, vol. 104, 1982, pages 4957-4958, XP000942669 ISSN: 0002-7863 compounds 19-21 page 4958 ---	1-5, 12-24
X	SAITO N ET AL: "SYNTHESIS OF SAFRAMYCINS X. TRANSFORMATION OF (-)-SAFRAMYCIN A TO (-)-SAFRAMYCIN MX TYPE COMPOUND WITH THE STRUCTURE PROPOSED FOR SAFRAMYCIN E" CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN. TOKYO, JP, vol. 43, no. 5, May 1995 (1995-05), pages 777-782, XP001037150 ISSN: 0009-2363 see compounds 9 and 12 ---	1-5, 12-23
X	SAITO ET AL.: "Synthesis of saframycins..." CHEM.PHARM.BULL., vol. 39, no. 5, 1991, pages 1343-1345, XP002206555 see compound 14 ---	1-5, 12-23
		-/-

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 01/47399

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SAKAI R ET AL: "ECTEINASCIDINS: PUTATIVE BIOSYNTHETIC PRECURSORS AND ABSOLUTE STEREOCHEMISTRY" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY, AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, US, vol. 118, 1996, pages 9017-9023, XP000942122 ISSN: 0002-7863 see page 9021-9022 ---	1-3,6,7, 12-22
P,X	MYERS ET AL.: "Synthesis and evaluation..." J.AM.CHEM.SOC., vol. 123, 8 May 2001 (2001-05-08), pages 5114-5115, XP002206556 the whole document ---	1-75
P,X	WO 01 53299 A (UNIV COLUMBIA) 26 July 2001 (2001-07-26) see pages 26,55,58 -----	1-75

INTERNATIONAL SEARCH REPORTInt'l application No.
PCT/US 01/47399**Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)**

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-2,4,6,8,10,12-18,21-32,65-75 (all part); 3,5,7,9,11,19,20,33-64

Remark on Protest The additional search fees were accompanied by the applicant's protest. No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-2,4,6,8,10,12-18,21-32,65-75 (all part); 3,5,7,9, 11,19,20,33-64

Compounds of formula I in which X1/X2 and X3/X4 are all bound to aromatic rings

2. Claims: 1-2,4,6,8,10,12-18,21-32,65-75 (all part)

Compounds of formula I in which X1/X2 and X3/X4 are not all bound to aromatic rings usefull as active agents

3. Claims: 76-82

Preparation of compounds of formula I

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2001/47399

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 0018233	A 06-04-2000	US 6124292 A		26-09-2000
		AU 6165099 A		17-04-2000
		EP 1117297 A1		25-07-2001
		JP 2002525296 T		13-08-2002
		WO 0018233 A1		06-04-2000
		US 6348467 B1		19-02-2002
JP 63002991	A 07-01-1988	NONE		
WO 0153299	A 26-07-2001	AU 3100301 A		31-07-2001
		WO 0153299 A1		26-07-2001
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